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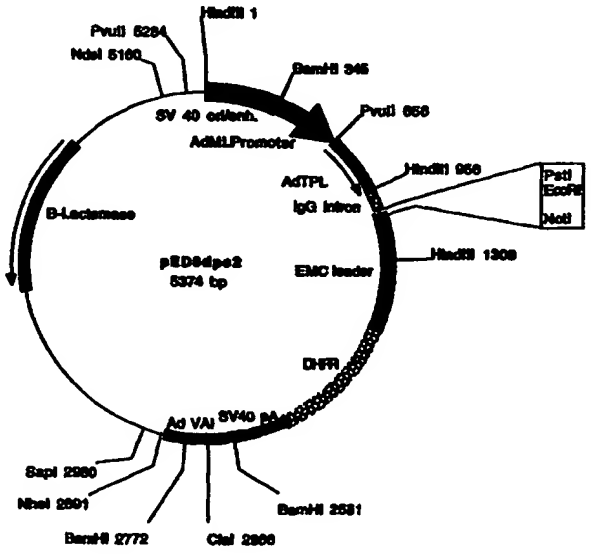
(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of application Ser. No. 08/887,195, filed July 2, 1997.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 516 to nucleotide 797;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 606 to nucleotide 797;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 773;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 516 to nucleotide 797; the nucleotide sequence of SEQ ID NO:1 from nucleotide 606 to nucleotide 797; the nucleotide sequence of SEQ ID NO:1 from

nucleotide 1 to nucleotide 773; the nucleotide sequence of the full-length protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 86.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 86;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 86.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 137 to nucleotide 1240;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 1153;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 137 to nucleotide 1240; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 1153; the nucleotide sequence of the full-length protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 339.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 339;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 339.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 26 to nucleotide 301;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 104 to nucleotide 301;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 119;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 26 to nucleotide 301; the nucleotide sequence of SEQ ID NO:5 from nucleotide 104 to nucleotide 301; the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 119; the nucleotide sequence of the full-length protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 31.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 31;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 31.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 663 to nucleotide 755;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 850;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone co36_1 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone co36_1 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 663 to nucleotide 755; the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 850; the nucleotide sequence of the full-length protein coding sequence of clone co36_1 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone co36_1 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 22.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 22;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 22.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 127 to nucleotide 783;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 172 to nucleotide 783;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 7 to nucleotide 462;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 127 to nucleotide 783; the nucleotide sequence of SEQ ID NO:9 from nucleotide 172 to nucleotide 783; the nucleotide sequence of SEQ ID NO:9 from nucleotide 7 to nucleotide 462; the nucleotide sequence of the full-length protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 112.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 112;

(c) fragments of the amino acid sequence of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 112.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 231 to nucleotide 533;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 231 to nucleotide 533; the nucleotide sequence of the full-length protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482. In other preferred

embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:12, SEQ ID NO:11 or SEQ ID NO:14 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) fragments of the amino acid sequence of SEQ ID NO:13; and

(c) the amino acid sequence encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 645 to nucleotide 782;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 10 to nucleotide 773;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 645 to nucleotide 782; the nucleotide sequence of SEQ ID NO:15 from nucleotide 10 to nucleotide 773; the nucleotide sequence of the full-length protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 43.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 43;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 43.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 94 to nucleotide 216;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 160 to nucleotide 216;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 193;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gc57_4 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone gc57_4 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 94 to nucleotide 216; the nucleotide sequence of SEQ ID NO:17 from nucleotide 160 to nucleotide 216; the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 193; the nucleotide sequence of the full-length protein coding

sequence of clone gc57_4 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone gc57_4 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 33.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 33;

(c) fragments of the amino acid sequence of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 33.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 943;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 670;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 943; the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 670; the nucleotide sequence of the full-length protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 223.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 223;

(c) fragments of the amino acid sequence of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 223.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 1242 to nucleotide 1457;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 1326 to nucleotide 1457;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 869 to nucleotide 1544;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 1242 to nucleotide 1457; the nucleotide sequence of SEQ ID NO:21 from nucleotide 1326 to nucleotide 1457; the nucleotide sequence of SEQ ID NO:21 from nucleotide 869 to nucleotide 1544; the nucleotide sequence of the full-length protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482; or the nucleotide sequence of the mature protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 69.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 69;

(c) fragments of the amino acid sequence of SEQ ID NO:22; and

(d) the amino acid sequence encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22 or the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 69.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of the pED6 and pNOTs vectors used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell

in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "bf228_14"

A polynucleotide of the present invention has been identified as clone "bf228_14". bf228_14 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bf228_14 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bf228_14 protein").

The nucleotide sequence of bf228_14 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bf228_14 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 18 to 30 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bf228_14 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for bf228_14 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bf228_14 demonstrated at least some homology with sequences identified as AA069549 (zm52e03.s1 Stratagene fibroblast (#937212) Homo sapiens cDNA clone 529276 3'), H83278 (yq49h09.r1 Homo sapiens cDNA clone 199169 5'), and N94898 (zb31b01.s1 Homo sapiens cDNA clone 305161 3' similar to contains Alu repetitive element;contains element MSR1 repetitive element). Based upon homology, bf228_14 proteins and each homologous protein or peptide may share at least some activity. The nucleotide sequence of bf228_14 indicates that it may contain an Alu repetitive element.

Clone "bg249_1"

A polynucleotide of the present invention has been identified as clone "bg249_1". bg249_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer

analysis of the amino acid sequence of the encoded protein. bg249_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bg249_1 protein").

The nucleotide sequence of bg249_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bg249_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bg249_1 should be approximately 2700 bp.

The nucleotide sequence disclosed herein for bg249_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bg249_1 demonstrated at least some homology with sequences identified as AA151021 (zl47c04.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 505062 5'), AA278781 (zs79a01.r1 Soares NbHTGBC Homo sapiens cDNA clone 703656 5'), R75099 (MDB1032R Mouse brain, Stratagene Mus musculus cDNA 5'end), and T06990 (EST04879 Homo sapiens cDNA clone HFBEB91). Based upon homology, bg249_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "bv286_1"

A polynucleotide of the present invention has been identified as clone "bv286_1". bv286_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. bv286_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "bv286_1 protein").

The nucleotide sequence of bv286_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the bv286_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 14 to 26 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 27, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone bv286_1 should be approximately 550 bp.

The nucleotide sequence disclosed herein for bv286_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. bv286_1 demonstrated at least some homology with sequences identified as AA132163 (zl38c07.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 504204 5' similar to WP:F55A11.1 CE05943 EF HAND DOMAINS), AA552888 (nk57h08.s1 NCI_CGAP_Pr7 Homo sapiens cDNA clone IMAGE:1017663 similar to WP:F55A11.1 CE05943 EF HAND DOMAINS), and H12316 (yj11d07.s1 Homo sapiens cDNA clone 148429 3' similar to SP:JS0027 JS0027 PROBABLE CALCIUM-BINDING PROTEIN). The predicted amino acid sequence disclosed herein for bv286_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted bv286_1 protein demonstrated at least some identity with sequences identified as L22647 (prostaglandin receptor ep1 subtype [Homo sapiens]). Based upon homology, bv286_1 proteins and each homologous protein or peptide may share at least some activity. The nucleotide sequence of bv286_1 indicates that it may contain an Alu repetitive element.

Clone "co36_1"

A polynucleotide of the present invention has been identified as clone "co36_1". co36_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. co36_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "co36_1 protein").

The nucleotide sequence of co36_1 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the co36_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone co36_1 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for co36_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "cp116_1"

A polynucleotide of the present invention has been identified as clone "cp116_1". cp116_1 was isolated from a human adult salivary gland cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cp116_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cp116_1 protein").

The nucleotide sequence of cp116_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cp116_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. Amino acids 3 to 15 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 16, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cp116_1 should be approximately 1600 bp.

The nucleotide sequence disclosed herein for cp116_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database.

Clone "cw1195_2"

A polynucleotide of the present invention has been identified as clone "cw1195_2". cw1195_2 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cw1195_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cw1195_2 protein").

The nucleotide sequence of the 5' portion of cw1195_2 as presently determined is reported in SEQ ID NO:11. An additional internal nucleotide sequence from cw1195_2 as presently determined is reported in SEQ ID NO:12. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:13. Additional nucleotide sequence from the 3' portion of cw1195_2, including the polyA tail, is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cw1195_2 should be approximately 3300 bp.

The nucleotide sequence disclosed herein for cw1195_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cw1195_2 demonstrated at least some homology with sequences identified as AA205460 (zq66f07.s1 Stratagene neuroepithelium (#937231) Homo sapiens cDNA clone 646597 3') and AA362052 (EST71451 MCF7 cell line Homo sapiens cDNA 5' end similar to EST containing Alu repeat). Based upon homology, cw1195_2 proteins and each homologous protein or peptide may share at least some activity. The nucleotide sequence of cw1195_2 indicates that it may contain an Alu repetitive element.

Clone "fh13_10"

A polynucleotide of the present invention has been identified as clone "fh13_10". fh13_10 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. fh13_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "fh13_10 protein").

The nucleotide sequence of fh13_10 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the fh13_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone fh13_10 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for fh13_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. fh13_10 demonstrated at least some homology with sequences identified as J00089 (Human Alu family interspersed repeat; clone BLUR6) and X00481 (Human non-alu family interspersed repeat). Based upon homology, fh13_10 proteins and each homologous protein or peptide may share at least some activity. The nucleotide sequence of fh13_10 indicates that it may contain a repetitive element.

Clone "gc57_4"

A polynucleotide of the present invention has been identified as clone "gc57_4". gc57_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. gc57_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "gc57_4 protein").

The nucleotide sequence of gc57_4 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the gc57_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 10 to 22 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 23, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone gc57_4 should be approximately 1900 bp.

The nucleotide sequence disclosed herein for gc57_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. gc57_4 demonstrated at least some homology with sequences identified as AA095328 (l3005.seq.F Fetal heart, Lambda ZAP Express Homo sapiens cDNA 5'), AA126440 (zk94e02.s1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 490490 3'), and Z82195 (Human DNA sequence from clone J274L71). Based upon homology, gc57_4 proteins and each homologous protein or peptide may share at least some activity. The nucleotide sequence of gc57_4 indicates that it may contain an Alu repetitive element.

Clone "h1165_3"

A polynucleotide of the present invention has been identified as clone "h1165_3". h1165_3 was isolated from a human adult blood (peripheral blood mononuclear cells treated with phytohemagglutinin and phorbol meristate acetate and mixed lymphocyte reaction) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of

the encoded protein. h1165_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "h1165_3 protein").

The nucleotide sequence of h1165_3 as presently determined is reported in SEQ ID NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the h1165_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone h1165_3 should be approximately 1250 bp.

The nucleotide sequence disclosed herein for h1165_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. h1165_3 demonstrated at least some homology with sequences identified as AA173098 (zp31d03.r1 Stratagene neuroepithelium (#937231) Homo sapiens cDNA clone 611045 5' similar to contains element TAR1 repetitive element), AA305139 (EST176159 Colon carcinoma (Caco-2) cell line II Homo sapiens cDNA 5' end), AA426375 (zv54h02.s1 Soares testis NHT Homo sapiens cDNA clone 757491 3'), and N72370 (yv38c11.r1 Homo sapiens cDNA clone 245012 5'). The predicted amino acid sequence disclosed herein for h1165_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted h1165_3 protein demonstrated at least some identity with sequences identified as U58758 (coded for by C. elegans cDNA yk83a5.3; coded for by C.elegans cDNA yk83a5.5 [Caenorhabditis elegans]). Based upon homology, h1165_3 proteins and each homologous protein or peptide may share at least some activity.

Clone "hb752_1"

A polynucleotide of the present invention has been identified as clone "hb752_1". hb752_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. hb752_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "hb752_1 protein").

The nucleotide sequence of hb752_1 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the hb752_1 protein corresponding to the foregoing

nucleotide sequence is reported in SEQ ID NO:22. Amino acids 16 to 28 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 29, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone hb752_1 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for hb752_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. hb752_1 demonstrated at least some homology with sequences identified as AA100979 (zm26f09.s1 Stratagene pancreas (#937208) Homo sapiens cDNA clone 526793 3'), AA490528 (aa51g11.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone 824516 3'), H65670 (yr72g12.r1 Homo sapiens cDNA clone 210886 5'), H86790 (ys72c03.s1 Homo sapiens cDNA clone 220324 3'), N58917 (yy61f11.s1 Homo sapiens cDNA clone 278061 3'), and Z43307 (H. sapiens partial cDNA sequence; clone c-18g09). Based upon homology, hb752_1 proteins and each homologous protein or peptide may share at least some activity.

Deposit of Clones

Clones bf228_14, bg249_1, bv286_1, co36_1, cp116_1, cw1195_2, fh13_10, gc57_4, h1165_3 and hb752_1 were deposited on July 2, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98482, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse

orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
bf228_14	SEQ ID NO:23
bg249_1	SEQ ID NO:24
bv286_1	SEQ ID NO:25
co36_1	SEQ ID NO:26
cp116_1	SEQ ID NO:27
cw1195_2	SEQ ID NO:28
fh13_10	SEQ ID NO:29
gc57_4	SEQ ID NO:30
h1165_3	SEQ ID NO:31
hb752_1	SEQ ID NO:32

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays

for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 32

(iv) CORRESPONDENCE ADDRESS:
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(D) STATE: MA
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(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 41,323

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1425 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCTAATTTGA GAAGAAAACA AGTAGGATTT TTGTTTTGTT TTGCATTTTG CAATATGGAG 60

GAGAAATGAT TAGACCTTAG GAAGTGCCAG TGGGTTGGTC CTTTCATGAA CATGCCATCA 120

GTAAAAGCCC TGGAAACAAG GTCATACCAG AGATTCATTG TGCCTTGTCA CAACTGCAAA 180

CAATATCTGA GTGGAATATT CAAAAACTTG CTTAGAAAGA AAACTCTAGG ACAGATGGCT 240

CCACTGAAGT TATTCCAAAT ATTTAATAAA TAAAGCATAC CAGGCTTTTA TAAACTCTTC 300

TAGAAGAAAA AAGTTGGAAC TTTTCCAATT CAGTTTTTCA GGCCAGTGCA ACCTTGATAC 360

CAAAACCAAT AAAACAAACA AACAAACAAA AAACATAAAG CTATAGACCA AAGTCTCATA 420

GATTTAGATG CAAAATCCTA AAATTGAAAA AAAAAGTCTA GTCATATCCA TAAACTGTAT 480

CATCACCAAG AGATGTTTAT TAGGGCAATC AAAAGATGAT TTATTATTTT TTAAAAAATC 540

AATGTGGCCT TCCCTTCCTC TTTCTTTTGA TTCCCCTCTT TGAGTTTTTA TGTGTCTCTT 600

TTGCCTTCCC TTCCCAGAGT GGAGGAGTTA GACCTGCATT GTGGGATGAG AGGAGTTGTG 660

GCTATGTGTC TGCTGGCACC AAGAGGGCTG AGGGTGAGGT GTGGAAGGGA CAGGGGGAGG 720

AGATGGGCAG CATTGTTAAG AGATTGGTAC CACTGAGCAA ATATGTTGAG AATGATGATG 780

GCAAGGTTTC TCCCTGTTAG AGAAGGTATT TGTAGAAATA GGAATGAGGA GAGCTAGAAA 840

ACCTGGAGTG TGGGATTAGA ATAGAACTCA TATCTTTTAA ATACATAGGA ACAATAGAGA 900

AATTGTTGGG TGTGCCCATA TACATATATT TTGTGATTCA TTCTACCGAG AGGACATAAA 960

TGCAGTCACA GCTCAGTAAC AGTAAACACA CCAACTGCCA AGTTATTATT TCCTAAATAC 1020

TATCCACAAA AAAGGGGACC AGGGATGATT CCTAGTCGGA GATTGGGAGA AAAAGAAGAT 1080

GAGCCTGAAT CATTTCATGT ACCTAACAGA AAGAAAATAC TCTGGCTGGG CTCAGWGGCT 1140

CATGTTTGTA ATTCTAGCAT GTTAGGAGGT CGAGGTGGGT GTGTTGCTTG AGCCCAGGAG 1200

TTTGAGACCA GCCCAGGCAA CATGGCAAAA CTGTCTCTAC AAAAAATATA AAAGTTAGCC 1260

AGGCGTGGTG GCATGCGCCT GTCGTCCGAG ATACTCGGGA GGCAGAGAGG TGGGAGGATC 1320

ACTTGAGCCT GGGAGATTGA GACTGCATCG AGCTGTGGTC ATGCCACTGC ACTCCAGCCT 1380

GGAGGACAGA GTGAGACCCT GTCTCAGGAA AAAAAAAAAA AAAAA 1425

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 94 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ile Tyr Tyr Phe Leu Lys Asn Gln Cys Gly Leu Pro Phe Leu Phe
1 5 10 15

Leu Leu Ile Pro Leu Phe Glu Phe Leu Cys Val Ser Phe Ala Phe Pro
20 25 30

Ser Gln Ser Gly Gly Val Arg Pro Ala Leu Trp Asp Glu Arg Ser Cys
35 40 45

Gly Tyr Val Ser Ala Gly Thr Lys Arg Ala Glu Gly Glu Val Trp Lys
50 55 60

Gly Gln Gly Glu Glu Met Gly Ser Ile Val Lys Arg Leu Val Pro Leu
65 70 75 80

Ser Lys Tyr Val Glu Asn Asp Asp Gly Lys Val Ser Pro Cys
85 90

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2859 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGCACCCAGC CGCGCCGGCG AGGACATGGG CAGCCGCGGC GCGCCCACCC CCCGCGCCGA 60

TGTGAATTAT TAAAAAGAAA ATGGCCCAAC GGAGCACTGT ATTTCCTTCT CGTGTCACCA 120

AGGAAAGGTA TAATATATGG AAAATATGCA TCTAAGGCGA GTGAGAACCA TGCCCCGACA 180

CAGCCAGTCC CTGACCATGG CACCATACTC ATCTGTAAGC CTCGTGGAGC AGCTGGAAGA 240

CAGGATCCTC TGCCATGAGA AAACCACCGC CGCCCTCGTA GAGCACGCCT TTCGGATTAA 300

AGATGACATT GTCAACAGTT TGCAGAAAAT GCAAAACAAA GGGGGAGGTG ACCGCTTGGC 360

CAGGCTTTTC TTGGAGGAGC ATATCAGAAA CATAACTGCC ATAGTGAAGC AACTTAATCG 420

GGATATCGAG GTACTCCAGG AGCAGATTCG TGCTCGGGAC AACATTAGCT ATGGAACTAA 480

TTCTGCCTTA AAGACCCTGG AGATGCGCCA GCTCTCCGGT TTGGGAGATC TTCGAGGAAG 540

AGTGGCAAGA TGTGATGCCA GCATAGCTAG ACTTTCTGCA GAGCACAAAA CGACCTATGA 600

GGGGCTCCAG CACTTGAACA AAGAACAGCA GGCTGCCAAA CTTATCTTGG AAACGAAAAT 660

CAAAGATGCA GAGGGACAGA TTTCTCAGCT TTTGAACAGA GTGGACTTGT CAATATCAGA 720

GCAGAGCACC AAACTGAAGA TGTCTCACAG AGACAGTAAC CACCAGCTTC AGCTTTTGGA 780

CACTAAATTT AAAGGTACAG TTGAGGAACT CAGTAACCAG ATATTATCTG CACGGAGTTG 840

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CTTGATTGTT AAGGAAAACA GTGGAGCCAG TGAAAGGGAT ATGGAGAAGA AGCTCAGCCA 960

GATGTCAGCC AGGCTTGACA AAATAGAAGA GGGTCAAAAG AAGACTTTTG ATGGTCAGAG 1020

AACAAGGCAA GAAGAGGAGA AGATGCACGG GCGAATCACC AAGCTGGAGT TACAGATGAA 1080

CCAGAACATC AAGGAAATGA AAGCAGAAGT TAATGCTGGG TTTACAGCCG TCTATGAAAG 1140

CATAGGATCC CTCAGGCAAG TTCTCGAGGC CAAGATGAAG CTGGACAGGG ACCAGCTACA 1200

GAAGCAAATC CAGCTGATGC AGAAGCCAGA GACCCCCATG TGAAGGGAGC TGGGACAAGG 1260

TCCTAAAAGA CAGTTTTGCC AGTGGGGCTA GGAGCCGGAT ACCTCTGTAG CCAGGCCATC 1320

GCTGCATTCA GGATTGTTCC ATCCATGGCG TGCATGTGCC AAGAAATGTG TTTTTATGGG 1380

TCTAAATGTT TACCTTGAGT CTTGAAAATA CTCTTTTGTT AAAAGTATGA AATACAGTTT 1440

TTACCAGTTT ATTTCACTTC TCTAAATTCA ATGGAAATCC CCCGCCCTGG ATTTTGAAAG 1500

GCTTTTATCT TCTTCATTTT ACGAATGGAA AGACGACAAT TTTTCTTCAA TGCTTGATGC 1560

ACTAATGAAG ACTGTTTACT ATTTTGAAAA ATGTCATGGG GATTTTTTTT TAATTAAGAA 1620

ACTAATGAAT CATCACAGGA ATGTGTTGCT CCTCACCCTA AATTAAGAGA ATGTCCCAGT 1680

AGATTAGACT TCAACCTTTG AGTCCAATTT GGATTTTATT ATCGTTGTCT ATGCACTTCT 1740

TATATTGGTT ATCTTCTTGT AAATCTTCTG TCTTTTGTAA GGGGAAAGGA TTTAACATTT 1800

AGAATAAACC CCACCATTTA TGTAATGGAA ATAGTTTAAA AATTGCTAAC TGCCATGTGG 1860

ATTGCAAATT AAATGGAAAC TTATTTAGAT AACGTAAGGC TCAATATCTG CGTTGACCAC 1920

CTAGATATTA CAGGTTTTAA TATTTAAAAC TATTTTTGAA TTATCCACAA CCTGTATAGT 1980

GATAGCCATA TATTTAATAA TGGAATGGTG GTTAACAGTC TATTTACTGC ACAATTAATT 2040

GTTCACTAAT CAAATAGAAT GTGGTAATTT TTCAGACTTT ATGATCTGTT TCCAAAATTG 2100

GCACAAAGTG CTAGGGTTTA TATACACTTA TCGTAACTGT ATTTTTGTGC CTTGGTTTTA 2160

TCATGTCAAT GCACTGTACT CTGTAAAAGT TTTGCAGACA AAATAGAAAG TATGATAATC 2220

CGTCAGAAGT ATGATGTAAA ACTGGAATCC TCTGTATTTT TTAAATGTTC TAAAAATTTT 2280

ATCGCTGTTA AGGTATTAAT CATTCAGTAT TACTAATGGA ATAGAAATTC ATACTTTTGT 2340

ATGGACAACA AATTGATATT GCATTTATAG CACTGTAAGA AACTTTCATC TTGAGCAACT 2400

TTGTAGATGA TGGGTGTTTT ATTTTCAATC GCCATATTTG ATCAGTCATT GAAAATTGGC 2460

CCCAGTGCTG TTTGTTCATC TCTGTATGTA AAAACTGACA GTGAGACACA ACTTTCTGAA 2520

CTGTGAGGGT GTCCCAGGAA AAAGAAAAAC AGGAATACTT TAACAATTAA AAAGAAAAAA 2580

ATGTTTTTTG TTTGCCAAGG ACTCAGGAAA ATAAAAAGCA TTTTCTATTT TTAGGACAAA 2640

TCACAAATGA AGTGTCTAAC TGGCTATTAC TGTTTACCCA TATAAAATAT GCTGCTAAAG 2700

TACATATTTT GCTGTCAATG GCTTGACAAT TTTTTTTTTC AAATTTGGAC ATGAGAGGTT 2760

ATATAGGGAC TATATTATCC AACACATATT TTCTTATTTT GCCACAAATT TCCACTTAAC 2820

AAATAAAAAA AGGCGAATGC TGTTTTGCAA AAAAAAAAA 2859

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 368 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Glu Asn Met His Leu Arg Arg Val Arg Thr Met Pro Arg His Ser
1 5 10 15

Gln Ser Leu Thr Met Ala Pro Tyr Ser Ser Val Ser Leu Val Glu Gln
20 25 30

Leu Glu Asp Arg Ile Leu Cys His Glu Lys Thr Thr Ala Ala Leu Val
35 40 45

Glu His Ala Phe Arg Ile Lys Asp Asp Ile Val Asn Ser Leu Gln Lys

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    50                  55                  60

Met Gln Asn Lys Gly Gly Gly Asp Arg Leu Ala Arg Leu Phe Leu Glu
65                  70                  75                  80

Glu His Ile Arg Asn Ile Thr Ala Ile Val Lys Gln Leu Asn Arg Asp
                85                  90                  95

Ile Glu Val Leu Gln Glu Gln Ile Arg Ala Arg Asp Asn Ile Ser Tyr
            100                 105                 110

Gly Thr Asn Ser Ala Leu Lys Thr Leu Glu Met Arg Gln Leu Ser Gly
        115                 120                 125

Leu Gly Asp Leu Arg Gly Arg Val Ala Arg Cys Asp Ala Ser Ile Ala
    130                 135                 140

Arg Leu Ser Ala Glu His Lys Thr Thr Tyr Glu Gly Leu Gln His Leu
145                 150                 155                 160

Asn Lys Glu Gln Gln Ala Ala Lys Leu Ile Leu Glu Thr Lys Ile Lys
                165                 170                 175

Asp Ala Glu Gly Gln Ile Ser Gln Leu Leu Asn Arg Val Asp Leu Ser
            180                 185                 190

Ile Ser Glu Gln Ser Thr Lys Leu Lys Met Ser His Arg Asp Ser Asn
        195                 200                 205

His Gln Leu Gln Leu Leu Asp Thr Lys Phe Lys Gly Thr Val Glu Glu
    210                 215                 220

Leu Ser Asn Gln Ile Leu Ser Ala Arg Ser Trp Leu Gln Gln Glu Gln
225                 230                 235                 240

Glu Arg Ile Glu Lys Glu Leu Leu Gln Lys Ile Asp Gln Leu Ser Leu
                245                 250                 255

Ile Val Lys Glu Asn Ser Gly Ala Ser Glu Arg Asp Met Glu Lys Lys
            260                 265                 270

Leu Ser Gln Met Ser Ala Arg Leu Asp Lys Ile Glu Glu Gly Gln Lys
        275                 280                 285

Lys Thr Phe Asp Gly Gln Arg Thr Arg Gln Glu Glu Glu Lys Met His
    290                 295                 300

Gly Arg Ile Thr Lys Leu Glu Leu Gln Met Asn Gln Asn Ile Lys Glu
305                 310                 315                 320

Met Lys Ala Glu Val Asn Ala Gly Phe Thr Ala Val Tyr Glu Ser Ile
                325                 330                 335

Gly Ser Leu Arg Gln Val Leu Glu Ala Lys Met Lys Leu Asp Arg Asp
            340                 345                 350
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Gln Leu Gln Lys Gln Ile Gln Leu Met Gln Lys Pro Glu Thr Pro Met
355 360 365

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 933 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TGCTTCGGAG ACCGTAAGGA TATTGATGAC CATGAGATCC CTGCTCAGAA CCCCCTTCCT 60

GTGTGGCCTG CTCTGGGCCT TTTGTGCCCC AGGCGCCAGG GCTGAGGAGC CTGCAGCCAG 120

CTTCTCCCAA CCCGGCAGCA TGGGCCTGGA TAAGAACACA GTGCACGACC AAGAGTACGT 180

ATTCAGCCCG GGCTGTGGTC CAGTGGCCTC CCCATCATCT GCAGCTGAGC CAGCGGCAAG 240

GGCATGCTCA GTCCTCCTTT CCTTCTTCCT GTTTCTATGG CTCCTTGACA TTCTTCAAGG 300

ATGATTCTTA TTCCTTATTG CCACCTATAA GTCAGGTATT CTTTTTTCAT CATTGTATCA 360

CAGGTGGAAG ATCTTTAGGC CCAAATGGGG CACATTACTT GTCTGAATCC GGTCTCTCCT 420

TTTTTTCACC ACAGACAGAC ACACACACAT ACAAATAGAC ACACAGGTAC ACATACACAG 480

TCATAGTAGC AGAATCCAGA AAATAGCTAA GGTTTCTTGA CTATAACAAG ACCTTTTTTA 540

AATCAACACA TTCAAACATT GAATCATTTG TTGCAGCTTT TGTCTTGGGC CAGTTAGCCT 600

CACGCATTAT ACTCGGTTAT CCTTTGTTTT TAAGGCTGGG TGCAGTGGCT CACACCTGTA 660

ATCCCAGTGC TTTGGGAGGC TGAGGCAGGT GGATTACTTG AGCCCAGGAA TTCGAGACCA 720

GCCTAGGCAA TATAGGGAAA ACCTGTCTCT AYTAAAAAAT TGCAAAAAAT TAGCTGGATG 780

TGGCAGTACA TGCCTATGGT CCCAGCTACT TGGGGGGCTG AAGTGGGAGA ATCAAMTGAG 840

CTTGGGAAGT TGAGGCTACA ATGAGCCAAG ATCACGCTCC TGCACTCCAG CCTGGGTGGC 900

AGAGTGAGAC CCTGTCTCAA AAAAAAAAA AAA 933

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 92 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Thr Met Arg Ser Leu Leu Arg Thr Pro Phe Leu Cys Gly Leu Leu
1 5 10 15

Trp Ala Phe Cys Ala Pro Gly Ala Arg Ala Glu Glu Pro Ala Ala Ser
20 25 30

Phe Ser Gln Pro Gly Ser Met Gly Leu Asp Lys Asn Thr Val His Asp
35 40 45

Gln Glu Tyr Val Phe Ser Pro Gly Cys Gly Pro Val Ala Ser Pro Ser
50 55 60

Ser Ala Ala Glu Pro Ala Ala Arg Ala Cys Ser Val Leu Leu Ser Phe
65 70 75 80

Phe Leu Phe Leu Trp Leu Leu Asp Ile Leu Gln Gly
85 90

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2956 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGTGTGTGGT GGTTTAAGAA TGTATATCAT AGGGTCAGGT GGCCTGGGTT CATTCCCCAG 60

CTACGTAACC TTTCTATGCC TGAGTTTCCT CATCTATAAA ACAAGGATAA TAATAGTGTG 120

TACTTCTTAG GATTGTTTTG GAGACTCATA AATGAGAAAT ACGTGAAAAA CTCCCTCAAG 180

GCAGTGCTTG ACACATAATG AGCACTCAGT TATCATGGTC ATCATGGTCA TCATCACTGC 240

TACCACCACT GCTGCTGCTA TTACCACTCT ACCTCTTCCC CCTGAAACTC TAATCACTTA 300

CCCTAGAAAC AGTTAAATTA CACTTCAGTG GGAAGGATCT CAGATTTCTT AATGGCACCT 360

GCATTTATAT AATGTTGATA TTGCACGTTC CTAGAAAACA TATCAAGAAG AAACCAAAAT 420

GTGTTTCTGT ACTTTGTAAA CCTGTACAAT AGTTAGAGAT TAGAGGACCT TTATAATCTA 480

CTACTAATTA CTGTGAAAGT AAACATTGTT TAATATACCA GTTCTTAAAG AAATATTTTG 540

TCTAGTCATT AATATTCTAG TTCATCTCAA AGCTTCCATT TGACAATTTA AAATTACTTA 600

AATTTTAATA TTAAAGGAAA CAGTTTTCCT GATTCTCATG AAAGTTCCTA TTTGCACTGA 660

AGATGACTAA ACCTTTTAGT CATAGTTTTA GAAGAATTGG CTTTTTTATA GCCATTTTAT 720

TTACATATGG GTACTGCATA GCAAAGGCAG CAGATTAGCC CTGTTTGTTT TGCAGGGATG 780

AAAGGTAGCA TTCCCAGAGA TTAAGTTGTT CTTGCTATTC CCATTCTCTG CTACATTTGC 840

CTACATTCTT TGGTCCTTTC TATTATTTGT TTCTTTGGTG GAATCCCCTT GTTGCTTATG 900

GCTGGATATT GTTATTCAGC AGATGAATCA CAAGTTTAGC CTGAGGGCCC TAAAGCATCA 960

GAAATAAATT AGAGCCGAGC AAAGTTTAAC TTCTCTGGAA CTTGCACCTT TAGTTTCCAT 1020

GTATTTCTGG AACCAAGATA TTTCAAAGGC TTACTTTATT TCAGACACCT ATTATCTTCA 1080

AGTCACAGAT AACTATTGAT TCTGTAAAGT GTTTCAAAGA TTTTTGTCCA CTAGACATTT 1140

TTAAATTTGT TCAACTCCTC CTCATCATTT TAGAAATTAT TTCTGTTAGG TAAAATTAAA 1200

ACTAACAATG TATTTTAGTT TATTTTTCTA ATGATACCAG TCACCTTTCG GGGCTAACTA 1260

AACATTTTGT GCAGCATTCT CTTAGTTTAC ATCCTCCTTT CTTTCAGTCT TCCTGTTTAT 1320

TAAGGCTGTC CTGTAGCAAA CAAAAGAGTG ACTCATGTTA AAAGTATTTT AACTGCTCTA 1380

ATATATCTGA GGAAGAATAA CTTTCTAAAT TAAAGTAATG TATTTTATTA AATATTAAAA 1440

TGCATTTTTT GGCTATTCAT TTCTGTATGT AAAAGAAAAG TTAACTTTAT GGTGTTATGC 1500

AAAATATGCT AAATTTAGAT TTTAGAGCAA TATATAGGGA GATATGTCAC AAATTTCTAC 1560

ATTTTGGTTA AATTATTAGT ATTTTTTTAT ATTCAAATGT GCCTTGATAT TTAAATAATA 1620

TACTGAATGC AGAATTTATG TTATGTGAAC CATTATGGAA AATGTTAATG TTAACAAAAT 1680

GAGGTGTATT GACTTTTCAA CAATGTAAAT TAAAGATGGT ACATCTACTG TTTAAGGGCA 1740

GAGGAATTAA AAGAGTATAG ATACTGAAAT GTATCACTTA CTAGTAGTGT GGCTATAATC 1800

AAATTAATTA ATCTCTCTCT AGGCTTTAGC TTCCTCATCT TAGTTTGTTC AGGCTACTGT 1860

AACAAAATAA CATAGATTAT GTACTTTTAA ATGACAGAAG TTTATTCGGC ATGGTTTGGG 1920

AGACTAGGAA GTCTAAGATT AAAGAACCAG CAAATTTGGT GTCTGATGAG GACCCATTCC 1980

TTTGTTCACA GATGATGCCT TCTCATTGTG TTTTCAAATG TTAGAAGGAG CTAGCTAGCT 2040

TTCTGGGGTC TCTTTTGTAA AGGCACTAAT CCCAGTCATT AGGGCAAATT GGCTCCTACA 2100

GGCCCCACCT ATCTCCTAAT ACCATCACCT TGAGGATTAA GATTTCTACA TATGAATGAA 2160

GCAGGTGTTG TAGAAGGTCA GTCAGTTAGA CCATAGCACC ATCTGTAAAA TTGAATAGTA 2220

ATTTACTGCC TCATTGGATG TCAGGATTAA AGGAGATAAG ATTTTATTAG TTACTAGTTA 2280

CCATAGTGGT TTTTTTTTTA CACTATAATG TTCGTTTTTT TGTTTCATGC TTGTACCTTC 2340

AACATTTCCT TCCATTTGAA TACTTCTTTT GTCTCCTGTA GGCCTGTCTG TCCACTTAGG 2400

TGTAAGATGT GTTTTTGTGT CAGGAATGAT GGTGCAATGC TAATGTTCCA TTGCCCTATT 2460

TGGCAATACT CTGATCATTA ACTATAAAGA ATAACACCAG TGTTAACTAA CTCTCCTTGC 2520

CTGACAGTAG TGCTGCCACT ATTCCTTGTT TCTGTGGTAA TAGATGAGGT TTGTATGGTC 2580

CTGTTATTCC AGCCTCCAGA CACCATTCCA GATCAACTGG TGCCYTCWAC GCCCCCGAAG 2640

TGTATGGGGC CTCAGGTGAA GGATGAGWAC ATTTTCACTA TCATCTGGCA TTCATCTCAG 2700

ATTTTATCCT TTTCAGTTTC CATTAAATAA TATTCATGTT TTAAAATTGA TTTTTTATTA 2760

TTTAAATTTA ATTTGTTGGA GAATAAACTT TTTTTTTTCT TTTCTCCCAA GTAACGTTTT 2820

CCCCTTTAGC AACTGTATTG AGCATTTTTC TCACTGGTAT ATGGACATTT TTTTGTATAA 2880

CCTGTTGTGT CATTTTTAAA TATAGAATTG TTTTTATGTT CTCATCTTTG TATATATGTT 2940

TAAAAAAAAA AAAAAA 2956

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Thr Lys Pro Phe Ser His Ser Phe Arg Arg Ile Gly Phe Phe Ile
1 5 10 15

Ala Ile Leu Phe Thr Tyr Gly Tyr Cys Ile Ala Lys Ala Ala Asp
20 25 30

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1325 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AATCGGGAAA AAAAGCCATG TATTCTTTCG TTTCTCTCTA AAAGAAGAAA AATATAATTT 60

AAAAATACAT TGCGTATTTT CTAAAACAAT AAATTTATAG TGTTAATATT CATAGGGTCA 120

ATCAAAATGA AGCTTCTCCT TTGGGCCTGC ATTGTATGTG TTGCTTTTGC AAGGAAGAGA 180

CGGTTCCCCT TCATTGGTGA GGATGACAAT GACGATGGTC ACCCACTTCA TCCATCTCTG 240

AATATTCCTT ATGGCATACG GAATTTACCA CCTCCTCTTT ATTATCGCCC AGTGAATACA 300

GTCCCCAGTT ACCCTGGGAA TACTTACACT GACACAGGGT TACCTTCGTA TCCCTGGATT 360

CTAACTTCTC CTGGATTCCC CTATGTCTAT CACATCCGTG GTTTTCCCTT AGCTACTCAG 420

TTGAATGTTC CTCCTCTCCC TCCTAGGGGT TTCCCGTTTG TCCCTCCTTC AAGGTTTTTT 480

TCAGCAGCTG CAGCACCCGC TGCCCCACCT ATTGCAGCTG AGCCTGCTGC AGCTGCACCT 540

CTTACATCCA CACCTGTAGC ATCTGAGCCT GCTGCAGGGG CCCCTGTTGC AGCTGAGCCT 600

GCTGCAGAGG CACCTGTTGG AGCTGAGCCT GCTGCAGAGG CACCTGTTGC AGCTGAGCCT 660

GCTGCAGAGG CACCTGTTGG AGTGGAGCCA GCTGCAGAGG AACCTTCACC AGCTGAGCCT 720

GCTACAGCCA AGCCTGCTGC CCCAGAACCT CACCCTTCTC CCTCTCTTGA ACAGGCAAAT 780

CAGTGAAATT CTCTAGAAGA GTACCATGGG TTCATTTCTA TACTGATGCA GAAATAAGTG 840

AAATCTACAA AAGTTTTCTT TCTTTTCCAA AGACTATTTC ATTCTGTAGT ATTCAGAGTA 900

TTCATCTCAC TACATAGATT TGTTTGTGGT AGTTATTTCC TTGGACTTAA TTTATATTGA 960

AAAAACATTG ATAATTAAAT AAATAAAATA GATAATTTAG ACCAATGGTG ATAAGGTCTG 1020

GATGAAAACT ACGCTATGGA GGACTGAAAT GGCAATCATT CAGCCTAGCC TGGAGTCTGA 1080

TTATACAGCT ACTATAGGAT GATGTTAGTA TTGGTTTTGA GTGCAATAGG TTTTTTCCTA 1140

AACAAACATA TTTTGTAGTC AATGAACTTT TTGTCACAAA ACAGTAAAAC ATCTGTGTTT 1200

AACCTATGGT AAACAACATG TTAATGAACT ATGCTATCCA TGACTTAATG GACAGTTCAA 1260

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1320

AAAAA 1325

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 219 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Lys Leu Leu Leu Trp Ala Cys Ile Val Cys Val Ala Phe Ala Arg
1 5 10 15

Lys Arg Arg Phe Pro Phe Ile Gly Glu Asp Asp Asn Asp Asp Gly His
20 25 30

Pro Leu His Pro Ser Leu Asn Ile Pro Tyr Gly Ile Arg Asn Leu Pro
35 40 45

Pro Pro Leu Tyr Tyr Arg Pro Val Asn Thr Val Pro Ser Tyr Pro Gly
50 55 60

Asn Thr Tyr Thr Asp Thr Gly Leu Pro Ser Tyr Pro Trp Ile Leu Thr
65 70 75 80

Ser Pro Gly Phe Pro Tyr Val Tyr His Ile Arg Gly Phe Pro Leu Ala
85 90 95

Thr Gln Leu Asn Val Pro Pro Leu Pro Pro Arg Gly Phe Pro Phe Val
100 105 110

Pro Pro Ser Arg Phe Phe Ser Ala Ala Ala Ala Pro Ala Ala Pro Pro
115 120 125

Ile Ala Ala Glu Pro Ala Ala Ala Ala Pro Leu Thr Ser Thr Pro Val
130 135 140

Ala Ser Glu Pro Ala Ala Gly Ala Pro Val Ala Ala Glu Pro Ala Ala
145 150 155 160

Glu Ala Pro Val Gly Ala Glu Pro Ala Ala Glu Ala Pro Val Ala Ala
165 170 175

Glu Pro Ala Ala Glu Ala Pro Val Gly Val Glu Pro Ala Ala Glu Glu
180 185 190

Pro Ser Pro Ala Glu Pro Ala Thr Ala Lys Pro Ala Ala Pro Glu Pro
195 200 205

His Pro Ser Pro Ser Leu Glu Gln Ala Asn Gln
210 215

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 225 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TGCGGGCTCA CANGAANAGT CTCACCTCAG TGCCAAGGGG TGTCAGAGAT GCTCACTGCC 60

CTCCTCTCCT TGGGGTTGCA TGNAGGCATG ATGGCGCTTG GCCGTGGCAG GGTAAGGAAC 120

CGGCGACNGA GGCCCATCAC GTGTTCACAT GCTCTCCTGC GTCNGTGCTT GGGAGATATG 180

GACTGTCNTG TCCTTAGACC ACATTTATNT CAAGGCAAGG GGAGC 225

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 533 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GGTTCAAAAT GAGGCAAAGA TAGGAAAGTG CTTCTTACAG ATAATTTTCA AGGCCAGTGA 60

CTGGAGAGAG GGGTAGGTCT GTCAATCGAG TGCTTGCTGA CTGCACATAT CACAGGGCGT 120

GTGACGACTG CTGGGAGAGG AAAGCGAGAC ATCATTCCAA CCCTCCAGAA GCTAAAGATC 180

CTGGAACTCA AGGGGAAAAC TAACGTAAGT GCGAAAGCGA ACAAGCAAAC ATGTCCTCAA 240

CGGGGCAGGC AGGCTGTCGG GGTACAGAGC TGGGATCTGG GAAGGAACAG AGAGGGCCGC 300

TCAGGGAGAG GAAGCACAGT GCCACCGGAG GCACGCACTC AGCAGGCACT CGCAGGCTGG 360

GCAGAGGTAG AGAAGCAGCG CTGCACAGGC AGGCAGCTGA CCCAGGGCTC TTAGAGCCGG 420

GCAGGAGAGC TGGTGTGGGA CCTGGGAGGA GGACAGGAGC CTTCAAAGCA GCACCGCCTG 480

ATTGCAGCCA GGAGGGTAGC ATCAAGGAAG ATGGAACTGC GGCCAGGCCA CAT 533

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Ser Ser Thr Gly Gln Ala Gly Cys Arg Gly Thr Glu Leu Gly Ser
1 5 10 15

Gly Lys Glu Gln Arg Gly Pro Leu Arg Glu Arg Lys His Ser Ala Thr
20 25 30

Gly Gly Thr His Ser Ala Gly Thr Arg Arg Leu Gly Arg Gly Arg Glu
35 40 45

Ala Ala Leu His Arg Gln Ala Ala Asp Pro Gly Leu Leu Glu Pro Gly
50 55 60

Arg Arg Ala Gly Val Gly Pro Gly Arg Arg Thr Gly Ala Phe Lys Ala
65 70 75 80

Ala Pro Pro Asp Cys Ser Gln Glu Gly Ser Ile Lys Glu Asp Gly Thr
85 90 95

Ala Ala Arg Pro His
100

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 458 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TAGGCAGTCA TCTTTGTAAA CCTCCACTGG TGCTGGCTGC GTTTAGAACA TACTCCATAT 60

AAAACAGGCC CTGGGATTAC AGGCATGAGC TACCGTGCCT GGCCCCCTTT TTTTTAATTA 120

CAGAGAAATA AGTTACACCT TAGTATCAGA TATTAATTTT CTTCAGTGTT CAGGCAATTA 180

GTATTTAGAA AGCTCTTGTC ATGAGATGGC TCTGGGATGT GATGATGATT GTTGGGATTG 240

AAAAAATGGT AGTATCATGG AGAGATCATA ATAAATTCTT AGTATTAAAA GTGGTTTTGC 300

TTTCAGTTAG GGAGAAAAAT TAGATTGTAC TATTTTTCCT CTATGATTTC CTTCAGTTAT 360

CTTCCAAATG TTGTTTTTTC CCCACAGCCC CCTTAACATT GTTCTCTATG CACTTCTCAA 420

TACATTTTCA TTTGTTTCTC AAAAAAAAAA AAAAAAAA 458

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1350 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TTTTTTTTTT TTTTTGTAGA GACAGGGTCT TGCCATTTTG CCCAGGTTGG TCTCAAACTT 60

CTGAGCTCAG GCTATCTGCC CACCTTGGCC TCCCAAAGTG CTGGGATTAC AGGTGTGAGC 120

CACTGTGCCC GGCCTGTATT GTTTTAAGTT ACACTTATTC CTTTTAAAAT TCAGAATTTG 180

TTAAGCATTT AAAACAAATT CATAAATTAA AACCTCCTTG AGATACCATT TACCATGTAG 240

TTTGATGAAC ATAATACATG GTGCATTACA TTGGCAAAAG CAGTGGGGAA AAAGATGCTT 300

TTATAAATGT CTGGTGGGAG TTAAATTGTG TAACTTCTAT TACACTTTTG TAATAGCTAC 360

CAAAATATGT TATTTCTATC TACCTCTCTC TCTCTGACTC AACAGTTCCA TTTCTAGGTT 420

TTGTGTTGTG GATATTCTTG AACATTGTGA AATGTATACA GGGAGGCTTC ACAGCAGCAC 480

TGTTTGTTTC AAATGATTTG AAAACAACCT CTCCATAAAC GAGATAGGCT AAATCAAGCA 540

TGGCACACCT ATACAATGGA TGCGGCCATT AAAAAGAACA AGGCAGCTCA TATGCATCAA 600

TATAAAAAGG TCTATAAACT ATACTATCAA ATGAAAATAG CAAGATGCTA CCATTTATAT 660

TAAAAAGAGG ACAAAATATT AATATATTCA TGGTTGCTTG TCTATGTGGA ATATTTCTGG 720

ATATATACAT AAGAAGTTAC ATTGGTTACC TATGGGCAGG TTACTACTGG GTGGCTTGTG 780

GGTGAGGGCA GGAAGAGCTT ACTTTCCATG GTAAACCTTT TTGTATATTT TGCAGCATTC 840

AAAAATTCTA ATTTAAAGTT TATTTTAGAA AAATGCCCCC ATGTATACAA GTGATTTCCA 900

AGTTCCTCCT TCAATATTTT TAATGATTAT GGAACACACT GAACTTCTTT TTTATTATTC 960

TAGCTGTGAA CTCTGTCTGC TGTCTACATG CACATATATA ATCTATGTAA TATTTAAATT 1020

TATATCCTTT ATATGTCAGT TGGGTGGTGA GTAAAAGAAA AATATATTTT TATCAGCAAA 1080

CTTGGTAAAT TGTTGAGGTT TCTGATATAG TCAGAGGTAG TTGCTTATCA CAACATTAGG 1140

TAAGTTTTTA AARACACCTA TTTAAAACAC ACTGATGTAT ATATATATTG GTCTGTTTTC 1200

ATGCTGCTGA TAAAGACATA TCCAAGACTG GGAAGAAAAA GAGGTTTAAT TGGGCTTATA 1260

GTTCCACATG GCTGGGGAGG CCTCAGAATC ATTGCGGGAG GCAAAAGGCA CTTCTTACAT 1320

GGCAGTGGCA AGAGAAAAAA AAAAAAAAAA 1350

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Leu Pro Phe Ile Leu Lys Arg Gly Gln Asn Ile Asn Ile Phe Met
1 5 10 15

Val Ala Cys Leu Cys Gly Ile Phe Leu Asp Ile Tyr Ile Arg Ser Tyr
20 25 30

Ile Gly Tyr Leu Trp Ala Gly Tyr Tyr Trp Val Ala Cys Gly
35 40 45

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1598 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TCGGGACACT ACATGAAGTC CTGAAAATAA CAGAGAAACT GTTATATCTT TTTAATGATT 60

TATTTGCAAG TATTGAGGTT GACCTGAAAA ACAATGAAAC ACATGAACAC ACTTCCGATT 120

TTCTCCTCGC TGATTAGCTT CCTGCCTGCT GTCAGTGCTG GACGAAGTGC TATAACTACT 180

TTATGTAACA TTACAGAACA GCTAGAGGTC CTGGGGTAAG AGAAAAAAAG CACATCACAA 240

CAAATGTGAA AGCCTTCATT ATTACACGTT CCAGTTTGTC TCGCTGTGTA GGCATAAGCT 300

AATGGTTTAT TTTCAGAAAG CTGCCTGAAA CGTTGCTTTG TATTCTTCTA GGAAGAACTT 360

TAATTCCTCC TGAGGAACTC TACTTTCTGA GCCAAACTGC TAATTTTCTG CGGAACTGTC 420

TAGAAGATCA TTCAAGAGAC CCTGCAGTTG CACTTTCTCG TAAAAGTTAA AAAAAAAAAA 480

AAAAAAAAAG GTTTTTCCCG GCCTTTGAAC ATTTTGCCTA TGAGAGTTTT GCATATATTT 540

TATACTTGAG TAGACAACTT TAATAATCCA TATTTATACT ATCGCAGAAG TAAGCATTTG 600

GCAAACGTTC AGCCATTAGC ACTCATTTAA CCCTGTTAGC AATATTCTTT TGAAAAAAGT 660

GCCAGTCCTT ATGTGATAAA CTAAGAAGCC CATTGAATAT AAAANTGTGT NGGACTGAAA 720

CNGTGACCTT ATATTATTGC TAAGGGAATA TGAGATTAAC TTCCTACAGG GGCCANAACC 780

ANANAAAGGC TTCCAGCAAC TTCGATNAAA NTANTTTGGC CACATNTCAA GCCAATTGTT 840

TGTACTATTT ATGTACCTTT TTCATAACTG GAATTGCCAA ATAAGCATGG AGATCTAAAT 900

GRAAAAAAAA AAAAAAAAAA AAAGCGGCCG CAGGTCTAGA ATTCAATCGG AAAAAACAAA 960

GAGAAGAAAC ATACTGCCCC ATCTTGTTTG CATGAAACTC TAGAATCTGG TGTTTCTCTA 1020

TTTATCTGCT CCCTCTTTGC CTACCTTGGN ATTTCTTTTT TTTTTTCTTT GTAACTATGG 1080

TTTTTACCTA AAGTTTAAAC TTTTTATTAT TATTTTCTCT CTAAATTCTT GCTAGTTAAT 1140

AACATTATTA ACTTCAAGAT TTTAGAAGAG CAGTGATGAT AGTAATGATC GATAACTAGA 1200

CTATCGAGTT TCAGAAGAAA CTTCCAAGTA TATATAATGT TTGACATAGC CTTTATTTCT 1260

ACAAATCTAC TACCTGTAAA CTAACATTTT AAAATACCTG TATATGGCTG GGTGTGGTGG 1320

CTTACACCTG TAATCCCAGC AGTTTGGGAG CCTGAGGTGG GCAGATTGCT TGAGCCCAGG 1380

AGTTGGAGAC AAGCCTGGAC AAAATAGACC TCTCTCTACA AAAAGTACAA AAAATTGGCT 1440

GGGTGTGGTG GCACACGCCT GTGGTCCCAG CTACTCGGGA GGCTGAGGTG GGAGGATTGC 1500

CTGAGCCCGG GAGATGGTGG TTGCAGTGAG CTGAGATCAC CCCATTGCAC TCCAGCCTGG 1560

ATAACAGAAT AAGATGCTGT CTTAAAAAAA AAAAAAAA 1598

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Lys His Met Asn Thr Leu Pro Ile Phe Ser Ser Leu Ile Ser Phe
1 5 10 15

Leu Pro Ala Val Ser Ala Gly Arg Ser Ala Ile Thr Thr Leu Cys Asn
20 25 30

Ile Thr Glu Gln Leu Glu Val Leu Gly
35 40

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1257 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CATGGCGTCC AGGTCTAAGC GGCGTGCCGT GGAAAGTGGG GTTCCGCAGC CGCCGGATCC 60

CCCAGTCCAG CGCGACGAGG AAGAGGAAAA AGAAGTCGAA AATGAGGATG AAGACGATGA 120

TGACAGTGAC AAGGAAAAGG ATGAAGAGGA CGAGGTCATT GACGAGGAAG TGAATATTGA 180

ATTTGAAGCT TATTCCCTAT CAGATAATGA TTATGACGGA ATTAAGAAAT TACTGCAGCA 240

GCTTTTTCTA AAGGCTCCTG TGAACACTGC AGAACTAACA GATCTCTTAA TTCAACAGAA 300

CCATATTGGG AGTGTGATTA AGCAAACGGA TGTTTCAGAA GACAGCAATG ATGATATGGA 360

TGAAGATGAG GTTTTTGGTT TCATAAGCCT TTTAAATTTA ACTGAAAGAA AGGGTACCCA 420

GTGTGTTGAA CAAATTCAAG AGTTGGTTMT ACGCTTCTGT GAGAAGAACT GTGAAAAGAG 480

CATGGTTGAA CAGCTGGACA AGTTTTTAAA TGACACCACC AAGCCTGTGG GCCTTCTCCT 540

AAGTGAAAGA TTCATTAATG TCCCTCCACA GATCGCTCTG CCCATGTACC AGCAGCTTCA 600

GAAAGAACTG KCGGGGGCAC ACAGAACCAA TAAGCCATGT GGGAAGTGCT ACTTTTACCT 660

TCTGATTAGT AAGACATTTG TGGAAGCAGG AAAAAACAAT TCCAAAAAGA AACCTAGCAA 720

CAAAAAGAAA GCTGCGTTAA TGTTTGCAAA TGCAGAGGAA GAATTTTTCT ATGAGAAGGC 780

AATTCTCAAG TTCAACTACT CAGTGCAGGA GGAGAGCGAC ACTTGTCTGG GAGGCAAATG 840

GTCTTTTGAT GACGTACCAA TGACGCCCTT GCGAACTGTG ATGTTAATTC CAGGCGACAA 900

GATGAACGAA ATCATGGATA AACTGAAAGA ATATCTATCT GTCTAACCCA TTTCCAATGG 960

ACAGTGATGG GCTTGTTTTT GTAAAATTAC CAGAAAACTC AGTGGAGATT TACTGAAAAA 1020

CTCAGACTTT ATTCAGATTA AGTTCCTCTA CAAAAAGTAG GGTTCTGTCC CATGTGTYTC 1080

TGACACATTT ACAAAATACC AGTTTTTTAA AATTTTGGTC AAATTATGAG TGGTTGATTT 1140

AAAAACTTTT CCAAGAAGAA GAAAAGCATG GAGTAGTAAT TTAAAGAACT CAATAAAAAC 1200

TTCTATTTTT TATTTTAAAA TAATAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAA 1257

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 314 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Ala Ser Arg Ser Lys Arg Arg Ala Val Glu Ser Gly Val Pro Gln
1 5 10 15

Pro Pro Asp Pro Pro Val Gln Arg Asp Glu Glu Glu Glu Lys Glu Val
20 25 30

Glu Asn Glu Asp Glu Asp Asp Asp Asp Ser Asp Lys Glu Lys Asp Glu
35 40 45

Glu Asp Glu Val Ile Asp Glu Glu Val Asn Ile Glu Phe Glu Ala Tyr
50 55 60

Ser Leu Ser Asp Asn Asp Tyr Asp Gly Ile Lys Lys Leu Leu Gln Gln
65 70 75 80

Leu Phe Leu Lys Ala Pro Val Asn Thr Ala Glu Leu Thr Asp Leu Leu
85 90 95

Ile Gln Gln Asn His Ile Gly Ser Val Ile Lys Gln Thr Asp Val Ser
100 105 110

Glu Asp Ser Asn Asp Asp Met Asp Glu Asp Glu Val Phe Gly Phe Ile
115 120 125

Ser Leu Leu Asn Leu Thr Glu Arg Lys Gly Thr Gln Cys Val Glu Gln
130 135 140

Ile Gln Glu Leu Val Xaa Arg Phe Cys Glu Lys Asn Cys Glu Lys Ser
145 150 155 160

Met Val Glu Gln Leu Asp Lys Phe Leu Asn Asp Thr Thr Lys Pro Val
165 170 175

Gly Leu Leu Leu Ser Glu Arg Phe Ile Asn Val Pro Pro Gln Ile Ala
180 185 190

Leu Pro Met Tyr Gln Gln Leu Gln Lys Glu Leu Xaa Gly Ala His Arg
195 200 205

Thr Asn Lys Pro Cys Gly Lys Cys Tyr Phe Tyr Leu Leu Ile Ser Lys
210 215 220

Thr Phe Val Glu Ala Gly Lys Asn Asn Ser Lys Lys Lys Pro Ser Asn
225 230 235 240

Lys Lys Lys Ala Ala Leu Met Phe Ala Asn Ala Glu Glu Glu Phe Phe
245 250 255

Tyr Glu Lys Ala Ile Leu Lys Phe Asn Tyr Ser Val Gln Glu Glu Ser
260 265 270

Asp Thr Cys Leu Gly Gly Lys Trp Ser Phe Asp Asp Val Pro Met Thr
275 280 285

Pro Leu Arg Thr Val Met Leu Ile Pro Gly Asp Lys Met Asn Glu Ile
290 295 300

Met Asp Lys Leu Lys Glu Tyr Leu Ser Val
305 310

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1544 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GCGGTCCTGC CACACAAGCT GGGCGGCGGA GGCCACGCAG CCGGGCCTTC TTCTCTCTGG 60

GACCCTCCGC CAGCGCATAG CCGCAGGCCG GTGTGACTTC TGCACCCTCG GTTCTGAGGG 120

TACGGTGACC CCTAGTGGGC AGTTTGCAAA ATGTGATTCC TTCTTCCCAA CTCCCCATCC 180

CCCCTTCCCT TCCCGTCACG TCCTGTTTGG GGGTTAATTC GGTTTTTTCT CTGTTGCATC 240

GCGCCTACTG TGCGTGTGCG ATARCGTGTG TGGGGGTGAG AGTTTGTTTT CTGGAATGGT 300

AGGTGCTGGG AGGAGGAGTT TGATGGAGGG CTTCCTGGCT GCTTCTGGCC CTCACCTCGT 360

GGAGGCCTTC ACAGAGACCC TGTGGGCCCT GGCCCTGTGC TGGCACTGTG CCAGTCATGA 420

GGCAGCTCTG ATCACTTCCC CACTGTGGAA ACAGGACTGA CCCAGCCTTC AGTGTGGGCT 480

GCTGAAGCTA TCCTCCTCAG GCCTCAGGGA TGACCTCCTG CCTGAGCCTC TCACAGGCTG 540

GCTGTGGGCC AGTTTCATCT GCTTTCCTGT TGGGGGTCCC GGGCCTCTGC TGTCCTTGAC 600

CCACTGGTGT TCTGTGCAAG GCTTCTTCCC ATTCACCAAG TGCACACCTT GCATCTGCCG 660

CTCGGCATGC ACCAGTTCCA CACACCATCC CATTTTACAG ACAAGGACGC TGAGGCCTGC 720

AGCAGCAGTG TGACTTGCTC AAGGTCCAGT GAGTGACCTC ATTCCCCAGA AAAGGCTCCT 780

CCCACACCAG AGTACAGCCT GGGTAGGGGG AAAATCAGTT CTTTCAGCTA CCACCCATCC 840

AACCTTTGGG CCTATGTGAA AAGAAAGGAA CTAAGCTGGG TGTGTTCTGT CTGGACCTGG 900

GGAGGCCCCT GAAGGCAAAG AGGGAAACTG TCCCAGCTGT TCTGTCCTAG GGGAGGGGGA 960

CATAGCCCTA GCAGGAGCTC CCAGCCCCTC TTGGCACTCT GACACACAAG TACACCCATC 1020

TGGGGCCCGC TTTGCCACGA AGAGCTGGGC AGGCCTGCAG GGTGTGGGGA AGGAGGACAC 1080

AACCTCAAGA AAGGAAGCGT GAACCCCAGG GAACAGCGGG TCCCTTCCCT CCTCAGACAC 1140

AAGCCACCTC AGCTTGTGGC TCTTGGCCCC CAGCCCCACC AACCCACCTG TTCATTTATT 1200

CAACAGACAA TGACAGCTGA TATTTATTGG ACATTTGCAC CATGCCAAGC ATTCGGCTTG 1260

GATTATCCCA TTTGTTTCTC ACAGCCGGTA TTTATTGTCT GCTCCTCTGT GCCAGGTGCT 1320

GTGCTCTGGG CAGGGGCACT GCATGGGCTG CCTGCCCTGG TGGAGCTTGT GGTCTGATGG 1380

GTGAGGCTGA CCCAAGCCCA CCCCATTGCC AACAGGGCCA GGGCAAGAGT ACACACAGGG 1440

GCCTCATACC ATATGTCTAA ATATTTAAAA GTTATCAATC AAGCTAACAA CTGTTAAATA 1500

AAATATGTTC TATTCTCCTA CTTTGAAAAA AAAAAAAAAA AAAA 1544

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Pro Ser Ile Arg Leu Gly Leu Ser His Leu Phe Leu Thr Ala Gly
1 5 10 15

Ile Tyr Cys Leu Leu Leu Cys Ala Arg Cys Cys Ala Leu Gly Arg Gly
20 25 30

Thr Ala Trp Ala Ala Cys Pro Gly Gly Ala Cys Gly Leu Met Gly Glu
35 40 45

Ala Asp Pro Ser Pro Pro His Cys Gln Gln Gly Gln Gly Lys Ser Thr
50 55 60

His Arg Gly Leu Ile Pro Tyr Val
65 70

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CNATGCAGGTC TAACTCCTCC ACTCTGGG 29

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

TNAGTTTGGTG CTCTGCTCTG ATATTGAC 29

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GNCATCAATAT CCTTACGGTC TCCGAAGC 29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GNAAATAGGAA CTTTCATGAG AATCAGGA 29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ANACAATGCAG GCCCAAAGGA GAAGCTTC 29

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GNTTGCTTGTT CGCTTTCGCA CTTACGTT 29

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucelotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ANTGGTAGCAT CTTGCTATTT TCATTTGA 29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TNGGAAGTGTG TTCATGTGTT TCATTGTT 29

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GNCCTCGTCCT CTTCATCCTT TTCCTTGT 29

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ANCACCTGGCA CAGAGGAGCA GACAATAA 29

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 516 to nucleotide 797;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 606 to nucleotide 797;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 773;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bf228_14 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein, which comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying the protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 86;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone bf228_14 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 86.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 137 to nucleotide 1240;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 1153;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bg249_1 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 339;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone bg249_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 26 to nucleotide 301;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 104 to nucleotide 301;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 119;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone bv286_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 31;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone bv286_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 663 to nucleotide 755;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 850;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone co36_1 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone co36_1 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 22;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone co36_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 127 to nucleotide 783;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 172 to nucleotide 783;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 7 to nucleotide 462;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cp116_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 112;

(c) fragments of the amino acid sequence of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone cp116_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 231 to nucleotide 533;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone cw1195_2 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) fragments of the amino acid sequence of SEQ ID NO:13; and

(c) the amino acid sequence encoded by the cDNA insert of clone cw1195_2 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:12, SEQ ID NO:11 or SEQ ID NO:14 .

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 645 to nucleotide 782;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 10 to nucleotide 773;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone fh13_10 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 43;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone fh13_10 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 94 to nucleotide 216;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 160 to nucleotide 216;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 193;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gc57_4 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone gc57_4 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 33;

(c) fragments of the amino acid sequence of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone gc57_4 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 943;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 2 to nucleotide 670;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone h1165_3 deposited under accession number ATCC 98482;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 223;

(c) fragments of the amino acid sequence of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone h1165_3 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 1242 to nucleotide 1457;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 1326 to nucleotide 1457;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 869 to nucleotide 1544;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone hb752_1 deposited under accession number ATCC 98482;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 69;

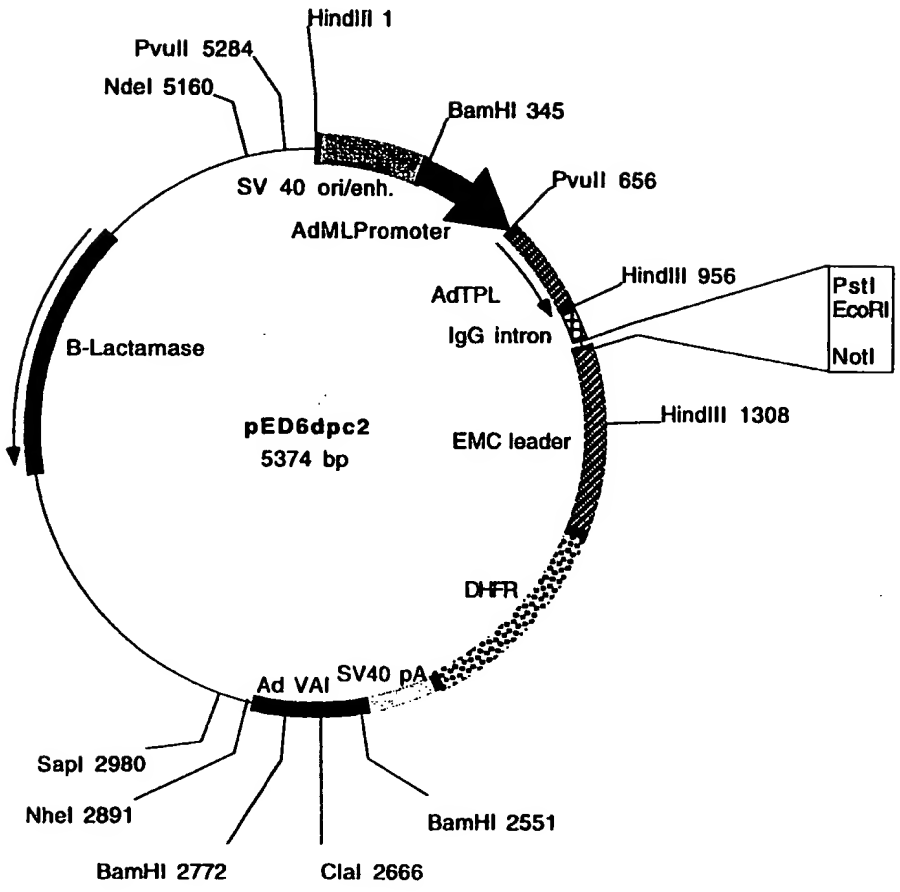
(c) fragments of the amino acid sequence of SEQ ID NO:22; and

(d) the amino acid sequence encoded by the cDNA insert of clone hb752_1 deposited under accession number ATCC 98482;

the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:21.

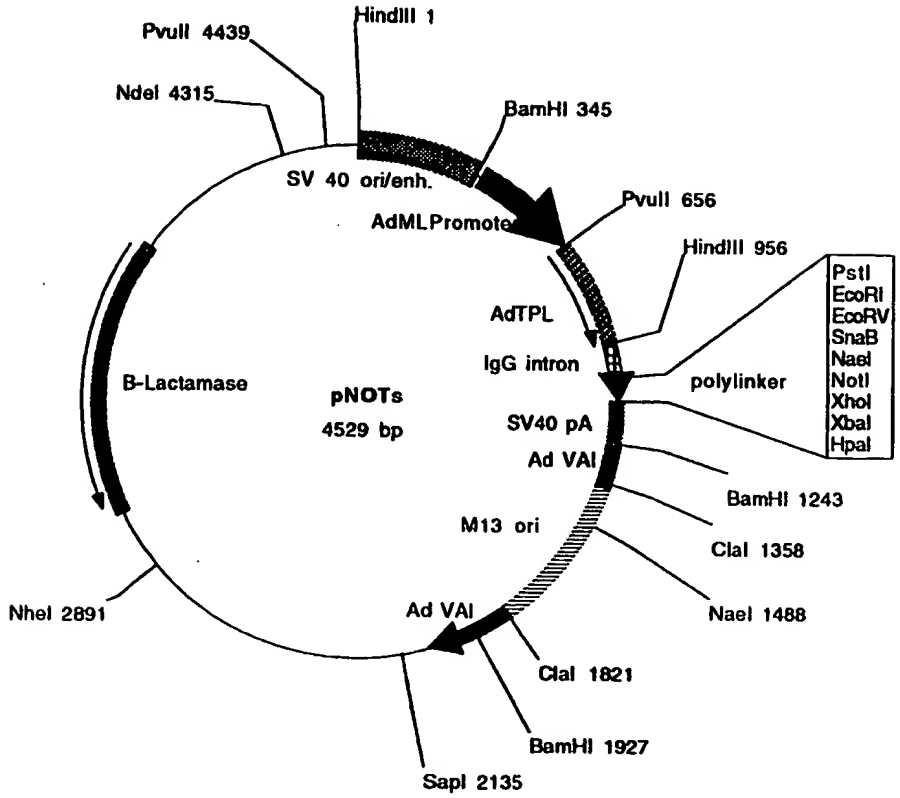
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13813

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07H 21/04; C07K 14/705; C12N 15/09, 15/63; C12Q 1/68
US CL : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CALLARD, R. E. et al. The Cytokine HandBook, London: Academic Press, Harcourt Brace and company publishers, 1994, pages 39-40, see entire document.	1-11
Y	REECK, G. R. et al. "Homology" in Protein and Nucleic Acids: A Terminology Muddle and a Way Out of it. Cell, 1987, Vol. 50, page 667, see entire document.	1-11
Y, P --- X, P	HILLIER, L et al. "zio3e04.rl Soares Fetal Liver Spleen 1NFLS S1 Homo Sapian cDNA clone 429726, 5', Embl-est Database, 9 May 1997, Accession No. AA11715.	1-11 --- 1
Y --- X	HILLIER, L et al. "yq49h09.rl Homosapians cDNA clone 199169 5', Embl-est Database, 13 November 1995, Accession No. H83278.	1-11 --- 1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
29 SEPTEMBER 1998

Date of mailing of the international search report
29 OCT 1998

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13813

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GEORGE, D. G. et al. Current Methods in Sequence Comparison and Analysis, Selected Methods and Applications. New York: Alan R. Liss, Inc., 1988, pages 124-129	1-11
Y	WO 94/01548 A2 (MEDICAL RESEARCH COUNCIL) 20 January 1994, see entire document.	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13813

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11 and 13

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13813

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, JAPIO, BIOSIS, SCISEARCH, WPIDS, EMBASE, EMBL-EST55, EMBL55, N-GENESEQ32, N-ISSUED, PIR56
bv 2271, atcc 98444, ac41-1, bf 228-14, secreted proteins, novel secreted proteins, SEQ ID NO:1, SEQ ID NO:2.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-11 and 13, drawn to composition of polynucleotides comprising SEQ ID NO:1, fragments thereof, allelic varients thereof, isolated gene thereof, host cell containing said polynucleotide, a process of producing the polypeptide encoded by polynucleotide of SEQ ID NO:2, encoded said polypeptide, polypeptide composition of said polypeptide.

Group II, claim 12 , drawn to method of preventing, treating or ameliorating a medical condition using the protein composition of SEQ ID NO:2.

Group III, claim(s) 14-16, drawn to composition of polynucleotide of SEQ ID NO:3, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:4, polynucleotide encoding SEQ ID NO:4, composition of of SEQ ID NO:4 of fragments thereof.

Group IV, claim(s) 17-19, drawn to composition of polynucleotide of SEQ ID NO:5, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:6, polynucleotide encoding SEQ ID NO:6, composition of of SEQ ID NO:6 of fragments thereof.

Group V, claim(s) 20-22, drawn to composition of polynucleotide of SEQ ID NO:7, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:8, polynucleotide encoding SEQ ID NO:8, composition of of SEQ ID NO:8 of fragments thereof.

Group VI, claim(s) 23-25, drawn to composition of polynucleotide of SEQ ID NO:9, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:10, polynucleotide encoding SEQ ID NO:10, composition of of SEQ ID NO:10 of fragments thereof.

Group VII, claim(s) 26-28, drawn to composition of polynucleotide of SEQ ID NO:11, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:12, polynucleotide encoding SEQ ID NO:12, composition of of SEQ ID NO:12 of fragments thereof.

Group VIII, claim(s) 29-31, drawn to composition of polynucleotide of SEQ ID NO:15, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:16, polynucleotide encoding SEQ ID NO:16, composition of of SEQ ID NO:16 of fragments thereof.

Group IX, claim(s) 32-34, drawn to composition of polynucleotide of SEQ ID NO:17, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:18, polynucleotide encoding SEQ ID NO:18, composition of of SEQ ID NO:18 of fragments thereof.

Group XI, claim(s) 35-37, drawn to composition of polynucleotide of SEQ ID NO:19, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:20, polynucleotide encoding SEQ ID NO:20,, composition of of SEQ ID NO:20 of fragments thereof.

Group XII, claim(s) 38-40, drawn to composition of polynucleotide of SEQ ID NO:21, sequences comprising same, varients thereof, polynucleotide hybridizing to all the afore mentioned, isolted gene corresponding to SEQ ID NO:22, polynucleotide encoding SEQ ID NO:22,, composition of of SEQ ID NO:22 of fragments thereof.

The inventions listed as Groups I-XI do not relate to a single inventive concept under PCT Rule 13.1 because, under

PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The main invention is Group I which is first product, first method of making the product and first method of using the product. Pursuant to 37 CFR 1.474 (d), these claims are considered by the ISA/US to constitute the main invention, and none of related groups II-XI correspond to the main invention.
The products of Groups III-XI do not share the same of corresponding special technical feature with Group I because they are drawn to products having materially different structures and functions, each defines a separate invention over the art.
The method of Group II, does not share the same or corresponding special technical feature with Group I because the methods of treatment use materially different compounds for materially different purposes, each defines a separate invention over the art.
Therefore, the claims are so linked by special technical feature within the meaning of PCT Rule 132.2 so as to form a single inventive concept.